Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
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L2	0	(plasmodium or malaria) same (in adj1 vivo) same (ex adj1 vivo)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/05 17:57
L3	0	(plasmodium or malaria) same (in adj1 vivo) same perfusion	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/05 17:57
L4	34	(plasmodium or malaria) same (in adj1 vivo) same blood	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/05 18:06
L5	0	(plasmodium or malaria) same (ex adj1 vivo) same (toxic or posionous)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/05 18:07
L6	70	(plasmodium or malaria) same (ex adj1 vivo)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/05 18:07
L7	0	(plasmodium or malaria) same (ex adj1 vivo) same toxic	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/05 18:07
L8	20	(plasmodium or malaria) same (ex adj1 vivo) and toxic	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/05 18:07
L9	1	(plasmodium or malaria) near10 (ex adj1 vivo) and toxic	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/05 18:09
L10	9	(plasmodium or malaria) near10 (ex adj1 vivo)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/04/05 18:09

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                  (ROSPATENT) added to list of core patent offices covered
 NEWS  4  FEB 28  PATDPAFULL - New display fields provide for legal status
                  data from INPADOC
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 NEWS  9  MAR 03  MEDLINE file segment of TOXCENTER reloaded
 NEWS  10 MAR 22  KOREAPAT now updated monthly; patent information enhanced
 NEWS  11 MAR 22  Original IDE display format returns to REGISTRY/ZREGISTRY
 NEWS  12 MAR 22  PATDPASPC - New patent database available
 NEWS  13 MAR 22  REGISTRY/ZREGISTRY enhanced with experimental property tags
 NEWS  14 APR 04  EPFULL enhanced with additional patent information and new
                  fields
 NEWS  15 APR 04  EMBASE - Database reloaded and enhanced

 NEWS EXPRESS  JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
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ENTER A FILE NAME OR (IGNORE):ignore
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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21
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FILE 'BIOTECHNO' ENTERED AT 16:03:29 ON 05 APR 2005

FILE 'CONFSCI' ENTERED AT 16:03:29 ON 05 APR 2005

FILE 'HEALSAFE' ENTERED AT 16:03:29 ON 05 APR 2005

FILE 'IMSDRUGCONF' ENTERED AT 16:03:29 ON 05 APR 2005

FILE 'LIFESCI' ENTERED AT 16:03:29 ON 05 APR 2005

FILE 'MEDICONF' ENTERED AT 16:03:29 ON 05 APR 2005

FILE 'PASCAL' ENTERED AT 16:03:29 ON 05 APR 2005


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=> (plasmodium or malaria) and (in vivo) and (nitric oxide)
L1            0 FILE AGRICOLA
L2           14 FILE BIOTECHNO
L3            1 FILE CONFSCI
L4            0 FILE HEALSAFE
L5            0 FILE IMSDRUGCONF
L6           22 FILE LIFESCI
L7            0 FILE MEDICONF
L8            4 FILE PASCAL

TOTAL FOR ALL FILES
L9           41 (PLASMODIUM OR MALARIA) AND (IN VIVO) AND (NITRIC OXIDE)

=> dup rem
ENTER L# LIST OR (END):12, 16, 18
PROCESSING COMPLETED FOR L2
PROCESSING COMPLETED FOR L6
PROCESSING COMPLETED FOR L8
L10          25 DUP REM L2, L6, L8 (15 DUPLICATES REMOVED)

=> d l10 ibib abs total

L10  ANSWER 1 OF 25  LIFESCI    COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER:   2005:18197  LIFESCI
TITLE:              Nitric Oxide Production and
                    Nitric Oxide Synthase Activity in
                    Malaria- Exposed Papua New Guinean Children and
                    Adults Show Longitudinal Stability and No Association with
                    Parasitemia
AUTHOR:             Boutlis, Craig S.; Weinberg, J. Brice; Baker, Joanne;
                    Bockarie, Moses J.; Mgone, Charles S.; Cheng, Qin; Anstey,
                    Nicholas M.
CORPORATE SOURCE:   International Health Program, Division of Infectious
                    Diseases, Menzies School of Health Research Institute of
                    Advanced Studies. Charles Darwin University, Darwin,
                    Northern Territory. Department of Drug Resistance and
                    Diagnostics, Australian Army Malaria Institute, Enoggera,
                    Queensland, Australia
SOURCE:             Infection and Immunity [Infect. Immun.], (20041200) vol.
```

72, no. 12, pp. 6932-6938.
ISSN: 0019-9567.
DOCUMENT TYPE: Journal
FILE SEGMENT: G; K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Individuals in areas of intense **malaria** transmission exhibit resistance (or tolerance) to levels of parasitemia in their blood that would normally be associated with febrile illness in **malaria** -naive subjects. The resulting level of parasitemia associated with illness (the pyrogenic threshold) is highest in childhood and lowest in adulthood. Clinical parallels between malarial and bacterial endotoxin tolerance have led to the supposition that both share common physiological processes, with **nitric oxide** (NO) proposed as a candidate mediator. The hypotheses that NO mediates tolerance and blood stage parasite killing in **vivo** were tested by determining its relationship to age and parasitemia cross-sectionally and longitudinally in a population of 195 children and adults from Papua New Guinea encountering intense **malaria** exposure. Despite pharmacological clearance of asymptomatic parasitemia, NO production and mononuclear cell NO synthase (NOS) activity were remarkably stable within individuals over time, were not influenced by parasitemia, and varied little with age. These results contrast with previous smaller cross-sectional studies. Baseline NO production and NOS activity did not protect against recurrent parasitemia, consistent with previous data suggesting that NO does not have antiparasitic effects against blood stage infection in **vivo** . The NO indices studied were markedly higher in specimens from study subjects than in samples from Australian controls, and NOS activity was significantly associated with plasma immunoglobulin E levels, consistent with induction of NO by chronic exposure to other infections and/or host genetic factors. These results suggest that NO is unlikely to mediate killing of blood stage parasites in this setting and is unlikely to be the primary mediator in the acquisition or maintenance of malarial tolerance.

L10 ANSWER 2 OF 25 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2005:16919 LIFESCI
TITLE: Suppression of **Plasmodium** chabaudi Parasitemia Is Independent of the Action of Reactive Oxygen Intermediates and/or **Nitric Oxide**
AUTHOR: Gillman, Brad M.; Batchelder, Joan; Flaherty, Patrick; Weidanz, William P.
CORPORATE SOURCE: Department of Medical Microbiology and Immunology, University of Wisconsin Medical School, Madison, Wisconsin
SOURCE: Infection and Immunity [Infect. Immun.], (20041100) vol. 72, no. 11, pp. 6359-6366.
ISSN: 0019-9567.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The killing of blood-stage **malaria** parasites in **vivo** has been attributed to reactive intermediates of oxygen (ROI) and of nitrogen (RNI). However, in the case of the latter, this contention is challenged by recent observations that parasitemia was not exacerbated in **nitric oxide** synthase (NOS) knockout (KO) (NOS2 super(-/-) or NOS3 super(-/-)) mice or in mice treated with NOS inhibitors. We now report that the time course shows that **Plasmodium** chabaudi parasitemia in NADPH oxidase KO (p47 super(phox-/-)) mice also was not exacerbated, suggesting a minimal role for ROI-mediated killing of blood-stage parasites. It is possible that the production of protective antibodies during **malaria** may mask the function of ROI and/or RNI. However, parasitemia in B-cell-deficient J sub(H) super(-/-) x NOS2 super(-/-) or J sub(H) super(-/-) x p47 super(phox-/-) mice was not exacerbated. In contrast, the magnitude of peak parasitemia was significantly enhanced in p47 super(phox-/-) mice treated with the xanthine oxidase inhibitor allopurinol, but the duration of patent parasitemia was not prolonged. Whereas the time course of parasitemia in NOS2 super(-/-) x p47 super(phox-/-) mice was nearly

identical to that seen in normal control mice, allopurinol treatment of these double-KO mice also enhanced the magnitude of peak parasitemia. Thus, ROI generated via the xanthine oxidase pathway contribute to the control of ascending P. chabaudi parasitemia during acute **malaria** but alone are insufficient to suppress parasitemia to subpatent levels. Together, these results indicate that ROI or RNI can contribute to, but are not essential for, the suppression of parasitemia during blood-stage **malaria**.

L10 ANSWER 3 OF 25 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2004:95497 LIFESCI
TITLE: Elevated **Nitric Oxide** Production in Children with Malarial Anemia: Hemozoin- Induced **Nitric Oxide** Synthase Type 2 Transcripts and **Nitric Oxide** in Blood Mononuclear Cells
AUTHOR: Keller, Christopher C.; Kremsner, Peter G.; Hittner, James B.; Misukonis, Mary A.; Weinberg, J. Brice; Perkins, Douglas J.
CORPORATE SOURCE: Department of Infectious Diseases and Microbiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania. Medical Research Unit, Albert Schweitzer Hospital, Lambarene, Gabon. Department of Parasitology, Institute for Tropical Medicine, University of Tuebingen, Tuebingen, Germany
SOURCE: Infection and Immunity [Infect. Immun.], (20040800) vol. 72, no. 8, pp. 4868-4873.
ISSN: 0019-9567.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Experiments outlined here investigate the role of **nitric oxide** (NO) in the pathogenesis of **Plasmodium** falciparum-induced malarial anemia (MA). The results show that ex **vivo** and in vitro NO synthase (NOS) activity in peripheral blood mononuclear cells (PBMCs) is significantly elevated in children with MA and inversely associated with hemoglobin levels. Additional experiments using PBMCs from non-**malaria**-exposed donors demonstrate that physiologic amounts of P. falciparum-derived hemozoin augment NOS type 2 (NOS2) transcripts and NO production. Results of these experiments illustrate that elevated NO production in children with MA is associated with decreased hemoglobin concentrations and that hemozoin can induce NOS2-derived NO formation in cultured blood mononuclear cells.

L10 ANSWER 4 OF 25 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2004:32164 LIFESCI
TITLE: Mice Deficient in Interleukin-4 (IL-4) or IL-4 Receptor alpha Have Higher Resistance to Sporozoite Infection with **Plasmodium** berghei (ANKA) than Do Naive Wild-Type Mice
AUTHOR: Saeftel, M.*; Krueger, A.; Arriens, S.; Heussler, V.; Racz, P.; Fleischer, B.; Brombacher, F.; Hoerauf, A.
CORPORATE SOURCE: Institute for Medical Parasitology, Friedrich Wilhelm University Bonn, 53105 Bonn, Germany; E-mail: saeftel@bni.uni-hamburg.de
SOURCE: Infection and Immunity [Infect. Immun.], (20040100) vol. 72, no. 1, pp. 322-331.
ISSN: 0019-9567.
DOCUMENT TYPE: Journal
FILE SEGMENT: F; G; K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB BALB/c interleukin-4 (IL-4 super(-/-)) or IL-4 receptor- alpha (IL-4r alpha super(-/-)) knockout (KO) mice were used to assess the roles of the IL-4 and IL-13 pathways during infections with the blood or liver stages of **plasmodium** in murine **malaria**. Intraperitoneal infection with the blood-stage erythrocytes of **Plasmodium**

berghei (ANKA) resulted in 100% mortality within 24 days in BALB/c mice, as well as in the mutant mouse strains. However, when infected intravenously with the sporozoite liver stage, 60 to 80% of IL-4 super(-/-) and IL- 4r alpha super(-/-) mice survived, whereas all BALB/c mice succumbed with high parasitemia. Compared to infected BALB/c controls, the surviving KO mice showed increased NK cell numbers and expression of inducible **nitric oxide** synthase (iNOS) in the liver and were able to eliminate parasites early during infection. In **vivo** blockade of NO resulted in 100% mortality of sporozoite-infected KO mice. In **vivo** depletion of NK cells also resulted in 80 to 100% mortality, with a significant reduction in gamma interferon (IFN- gamma) production in the liver. These results suggest that IFN- gamma -producing NK cells are critical in host resistance against the sporozoite liver stage by inducing NO production, an effective killing effector molecule against **Plasmodium**. The absence of IL-4-mediated functions increases the protective innate immune mechanism identified above, which results in immunity against P. berghei infection in these mice, with no major role for IL-13.

L10 ANSWER 5 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 2003:36263185 BIOTECHNO
TITLE: Gene gun-based co-immunization of merozoite surface protein-1 cDNA with IL-12 expression plasmid confers protection against lethal **Plasmodium** yoelii in A/J mice
AUTHOR: Sakai T.; Hisaeda H.; Nakano Y.; Zhang M.; Takashima M.; Ishii K.; Maekawa Y.; Matsumoto S.; Nitta Y.; Miyazaki J.-I.; Yamamoto S.; Himeno K.
CORPORATE SOURCE: T. Sakai, Dept. of Parasitology and Immunology, Univ. of Tokushima Sch. of Medicine, Tokushima 770-8503, Japan.
E-mail: buri@basic.med.tokushima-u.ac.jp
SOURCE: Vaccine, (28 MAR 2003), 21/13-14 (1432-1444), 60 reference(s)
CODEN: VACCDE ISSN: 0264-410X
PUBLISHER ITEM IDENT.: S0264410X02006655
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English

AN 2003:36263185 BIOTECHNO
AB The carboxyl-terminal region of the merozoite surface protein-1 (MSP1) is a leading candidate for a vaccine against **malaria** in the erythrocytic stage. In this study, we investigated the utility of interleukin-12 (IL-12) cDNA as an adjuvant for **malaria** DNA vaccine in a mouse challenge model. We found that co-immunization of expression plasmids encoding a C-terminal 15-kDa fragment of MSP1 (MSP1-15) with the IL-12 gene using a gene gun significantly increased the protective immunity against **malaria** as compared with MSP1-15 DNA immunization alone. Co-immunization of IL-12 DNA potentiated MSP1-15-specific T helper (Th)1-type immune responses as evaluated by **in vivo** antibody (Ab) responses and in vitro cytokine profiles. After the **Plasmodium** yoelii challenge, mice immunized with MSP1-15 plus IL-12 DNA showed a higher level of interferon gamma (IFN-γ) production than did other groups of mice. **In vivo** neutralization of IFN-γ or depletion of CD4.sup.+ T cells completely abolished this protective immunity. Macrophages, but not **nitric oxide** (NO), were found to play an important role in this effector mechanism. The sera from mice in which the infection had been cleared by the vaccination showed strong protection against P. yoelii infection. Thus, in addition to cellular immune responses, Abs against parasites induced in the course of infection are essential for protection against P. yoelii. The results indicate that combined vaccination with DNA encoding antigenic peptides plus IL-12 DNA provides a strategy for improving the prophylactic efficacy of a vaccine for **malaria** infection. .COPYRGT. 2002 Elsevier Science Ltd. All rights reserved.

L10 ANSWER 6 OF 25 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2004:63070 LIFESCI
TITLE: Inducible **nitric oxide** synthase (NOS2) promoter ccttt repeat polymorphism: Relationship to in **vivo nitric oxide** production/NOS activity in an asymptomatic **malaria** -endemic population
AUTHOR: Boutlis, C.S.; Hobbs, M.R.; Marsh, R.L.; Misukonis, M.A.; Tkachuk, A.N.; Lagog, M.; Booth, J.; Granger, D.L.; Bockarie, M.J.; Mgone, C.S.; Levesque, M.C.; Weinberg, J.B.; Anstey, N.M.
CORPORATE SOURCE: International Health Program, Infectious Diseases Division, Menzies School of Health Research, PO Box 41096, Casuarina, Darwin, Northern Territory, 0811, Australia; E-mail: anstey@menzies.edu.au
SOURCE: American Journal of Tropical Medicine and Hygiene [Am. J. Trop. Med. Hyg.], (20031200) vol. 69, no. 6, pp. 569-573. ISSN: 0002-9637.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Polymorphisms in the inducible **nitric oxide** synthase gene (NOS2) promoter have been associated with clinical outcome from **malaria**. These include a CCTTT repeat (CCTTT sub(n)) 2.5 kilobases upstream from the NOS2 transcription start site, and two single nucleotide substitutions: G arrow right C at position -954 (G-954C), and C arrow right T at position -1173 (C-1173T). Although hypothesized to influence NO production in **vivo**, the functional relevance of (CCTTT) sub(n) and G-954C is uncertain because disease association studies have yielded inconsistent results. This study found no association between CCTTT repeat number and levels of plasma NO metabolites or peripheral blood mononuclear cell NOS activity in a cohort of asymptomatic **malaria**-exposed coastal Papua New Guineans 1-60 years old. This suggests that (CCTTT) sub(n) does not independently influence NOS2 transcription in **vivo** . Neither the G-954C nor the C-1173T polymorphisms were identified in this population, indicating the variability and complexity of selection for NOS2 promoter polymorphisms in different **malaria**-endemic populations.

L10 ANSWER 7 OF 25 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2003:104970 LIFESCI
TITLE: Pharmacological assessment of the role of **nitric oxide** in mice infected with lethal and nonlethal species of **malaria**
AUTHOR: Dascombe, M.J.*; Nahrevanian, H.
CORPORATE SOURCE: 3164 Tehran, Iran; E-mail: mike.dascombe@man.ac.uk) Hossein Nahrevanian, Department of Parasitology, Pasteur Institute of Iran, Pasteur Avenue, 13164 Tehran, Iran
SOURCE: Parasite Immunology [Parasite Immunol.], (20030300) vol. 25, no. 3, pp. 149-159. ISSN: 0141-9838.
DOCUMENT TYPE: Journal
FILE SEGMENT: F; K
LANGUAGE: English
SUMMARY LANGUAGE: English
AB This pharmacological investigation sought to determine whether **nitric oxide** (NO) had an antiparasitic effect and/or mediated pathology in mice infected with nonlethal P. chabaudi or lethal P. berghei. **Nitric oxide** synthase (NOS) inhibitors were evaluated for their ability to inhibit the rise in reactive nitrogen intermediates (RNI) induced by bacterial lipopolysaccharide (LPS) in mice. The more effective compound, aminoguanidine (AG) inhibited the rise in RNI induced by P. chabaudi and increased mortality, but had no effect on parasitaemia. Inducers and donors of NO were screened for their ability to increase RNI and the most effective agents evaluated for their ability to modify P. berghei infection. S-Nitrosoglutathione had little effect, but

LPS decreased parasitaemia and mortality. An inconsistent relationship is evident between the abilities of these agents to modify NO activity and their effects on **malaria** in mice. Increased mortality in mice with P. chabaudi treated with AG indicates a reduction in resistance. The absence of an effect on parasitaemia by a NOS inhibitor or NO donor indicates either RNI have insignificant antimalarial action in **vivo** or the efficacy of the compounds is inadequade. Resistance to P. berghei in LPS-treated mice demonstrates an antiparasitic effect, but this may be attributable to factors other than NO.

L10 ANSWER 8 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 2001:32187621 BIOTECHNO
TITLE: Interleukin-12- and gamma interferon-dependent protection against **malaria** conferred by CpG oligodeoxynucleotide in mice
AUTHOR: Gramzinski R.A.; Doolan D.L.; Sedegah M.; Davis H.L.; Krieg A.M.; Hoffman S.L.
CORPORATE SOURCE: S.L. Hoffman, Malaria Program, Naval Medical Research Center, 503 Robert Grant Ave., Silver Spring, MD 20910-7500, United States.
E-mail: hoffmans@nmrc.navy.mil
SOURCE: Infection and Immunity, (2001), 69/3 (1643-1649), 39 reference(s)
CODEN: INFIBR ISSN: 0019-9567
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32187621 BIOTECHNO
AB Unmethylated CpG dinucleotides in bacterial DNA or synthetic oligodeoxynucleotides (ODNs) cause B-cell proliferation and immunoglobulin secretion, monocyte cytokine secretion, and activation of natural killer (NK) cell lyric activity and gamma interferon (IFN-γ) secretion **in vivo** and in vitro. The potent Th1-like immune activation by CpG ODNs suggests a possible utility for enhancing innate immunity against infectious pathogens. We therefore investigated whether the innate immune response could protect against **malaria**. Treatment of mice with CpG ODN 1826 (TCCATGACGTTCCTGACGTT, with the CpG dinucleotides underlined) or 1585 (ggGGTCAACGTTGAgggggG, with g representing diester linkages and phosphorothioate linkages being to the right of lowercase letters) in the absence of antigen 1 to 2 days prior to challenge with **Plasmodium** yoelii sporozoites conferred sterile protection against infection. A higher level of protection was consistently induced by CpG ODN 1826 compared with CpG ODN 1585. The protective effects of both CpG ODNs were dependent on interleukin-12, as well as IFN-γ. Moreover, CD8.sup.+ T cells (but not CD4.sup.+ T cells), NK cells, and **nitric oxide** were implicated in the CpG ODN 1585-induced protection. These data establish that the protective mechanism induced by administration of CpG ODN 1585 in the absence of parasite antigen is similar in nature to the mechanism induced by immunization with radiation-attenuated P. yoelii sporozoites or with plasmid DNA encoding preerythrocytic-stage P. yoelii antigens. We were unable to confirm whether CD8.sup.+ T cells, NK cells, or **nitric oxide** were required for the CpG ODN 1826-induced protection, but this may reflect differences in the potency of the ODNs rather than a real difference in the mechanism of action of the two ODNs. This is the first report that stimulation of the innate immune system by CpG immunostimulatory motifs can confer sterile protection against **malaria**.

L10 ANSWER 9 OF 25 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2002:7174 LIFESCI
TITLE: **Nitric oxide** and reactive nitrogen intermediates during lethal and nonlethal strains of murine **malaria**
AUTHOR: Nahrevanian, H.; Dascombe, M.J.*

CORPORATE SOURCE: School of Biological Sciences, The University of Manchester, Manchester, UK; E-mail: mdascomb@fs1.scg.man.ac.uk
SOURCE: Parasite Immunology [Parasite Immunol.], (20010900) vol. 23, no. 9, pp. 491-501.
ISSN: 0141-9838.
DOCUMENT TYPE: Journal
FILE SEGMENT: F; K
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The virulence of **Plasmodia** depends partly on the strain of parasite and partly on the host. In this study, **Plasmodium** berghei N/13/1A/4/203 caused the death of mice, whereas **Plasmodium** chabaudi chabaudi AS was not lethal. Current opinion is that **nitric oxide** (NO) and other reactive nitrogen intermediates (RNI) are produced in several host organs during **malaria** to resist infection or produce tissue damage. NO and RNI production in blood or plasma, brain, liver and spleen in MF1 mice was investigated during P. berghei and P. c. chabaudi infection, in order to help determine whether changes in NO production are beneficial or detrimental to the host in **vivo**. NO production was measured both directly and indirectly as nitrites and nitrates, to represent RNI. No changes in blood NO were detected in P. berghei infected mice, but increases were observed in brain, liver and spleen. In P. c. chabaudi infected mice, rises in NO concentration were observed in blood and spleen, whereas a decline in liver NO was seen, but there were no changes in brain. Liver contained the highest concentration of RNI, but increasing concentrations were seen in both plasma and spleen in both P. berghei and P. c. chabaudi infected mice. These results show that NO and RNI production alters during murine **malaria**. The changes depend upon the tissue, the day of infection, the degree of parasitaemia, the strain of **Plasmodia** and the method of measuring NO biosynthesis. Lethal P. berghei induced NO production in the mid and late stages of infection in mice when parasitaemia was high, whereas in nonlethal P. c. chabaudi infection, NO production was increased in the early and late stages when parasitaemia was low. These data are consistent with a role for NO in the protection of the MF1 mouse against **Plasmodia**. Failure to clear the parasite is associated with evidence of increased NO production in brain and liver, which may contribute to the pathology of **malaria** , but this hypothesis requires confirmation from other experimental approaches.

L10 ANSWER 10 OF 25 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2001:89440 LIFESCI
TITLE: **Nitric oxide** synthase 2 super(Lambarene) (G-954C), increased **nitric oxide** production, and protection against **malaria**
AUTHOR: Kun, J.F.; Mordmuller, B.; Perkins, D.J.; May, J.; Mercereau-Puijalon, O.; Alpers, M.; Weinberg, J.B.; Kremsner, P.G.
CORPORATE SOURCE: Department of Parasitology, Institute for Tropical Medicine, University of Tubingen, Tubingen, Germany
SOURCE: Journal of Infectious Diseases [J. Infect. Dis.], (20010801) vol. 184, no. 3, pp. 330-336.
ISSN: 0022-1899.
DOCUMENT TYPE: Journal
FILE SEGMENT: K
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A point mutation in the promoter of the **nitric oxide** synthase 2 gene (NOS2), termed NOS2 super(Lambarene) (NOS2-G954C), protects heterozygous carriers against severe **malaria** as effectively as the sickle cell trait. In a prospective longitudinal study, 841 individual infections of initially 200 children (151 wild-type vs. 49 NOS2 super(Lambarene) carriers) were monitored for 4 years, to assess the rates of malarial attacks in the 2 groups; carriers of the NOS2 super(Lambarene) polymorphism were significantly less likely to experience

malarial attacks than were others (P = 0.002). The distribution of the NOS2 super(Lambarene) polymorphism was investigated in **malaria** -endemic areas. It was found to be present with the highest frequency in Africa and at a lower frequency in Asia. Ex **vivo** studies showed that cells isolated from people with this polymorphism have a 7-fold higher baseline NOS activity, compared with the levels detected in cells from subjects with the wild-type gene (P = 0.003).

L10 ANSWER 11 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 2000:30497704 BIOTECHNO
TITLE: Central role of endogenous gamma interferon in protective immunity against blood-stage **Plasmodium** chabaudi AS infection
AUTHOR: Su Z.; Stevenson M.M.
CORPORATE SOURCE: M.M. Stevenson, Montreal General Hospital, Research Institute, 1650 Cedar Ave., Montreal, Que. H3G 1A4, Canada.
E-mail: mcev@musica.mcgill.ca
SOURCE: Infection and Immunity, (2000), 68/8 (4399-4406), 47 reference(s)
CODEN: INFIBR ISSN: 0019-9567
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:30497704 BIOTECHNO
AB The role of endogenous gamma interferon (IFN-γ) in protective immunity against blood-stage **Plasmodium** chabaudi AS **malaria** was studied using IFN-α gene knockout (GKO) and wild-type (WT) C57BL/6 mice. Following infection with 10.sup.6 parasitized erythrocytes, GKO mice developed significantly higher parasitemia during acute infection than WT mice and had severe mortality. In infected GKO mice, production of interleukin 12 (IL-12) p70 and tumor necrosis factor alpha **in vivo** and IL-12 p70 in vitro by splenic macrophages was significantly reduced compared to that in WT mice and the enhanced **nitric oxide** (NO) production observed in infected WT mice was completely absent. WT and GKO mice had comparable numbers of total nucleated spleen cells and B220.sup.+ and Mac-1.sup.+ spleen cells both before and after infection. Infected WT mice, however, had significantly more F4/80.sup.+, NK1.1.sup.+, and F4/80.sup.+Ia.sup.+ spleen cells than infected GKO mice; male WT had more CD3.sup.+ cells than male GKO mice. In comparison with those from WT mice, splenocytes from infected GKO mice had significantly higher proliferation in vitro in response to parasite antigen or concanavalin A stimulation and produced significantly higher levels of IL-10 in response to parasite antigen. Infected WT mice produced more parasite-specific immunoglobulin M (IgM), IgG2a, and IgG3 and less IgG1 than GKO mice. Significant gender differences in both GKO and WT mice in peak parasitemia levels, mortality, phenotypes of spleen cells, and proliferation of and cytokine production by splenocytes in vitro were apparent during infection. These results thus provide unequivocal evidence for the central role of endogenous IFN-γ in the development of protective immunity against blood-stage P. chabaudi AS.

L10 ANSWER 12 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2000:30444864 BIOTECHNO
TITLE: Direct immunization of **malaria** DNA vaccine into the liver by gene gun protects against lethal challenge of **Plasmodium** berghei sporozoite
AUTHOR: Yoshida S.; Kashiwamura S.-I.; Hosoya Y.; Luo E.; Matsuoka H.; Ish II A.; Fujimura A.; Kobayashi E.
CORPORATE SOURCE: S. Yoshida, Department of Medical Zoology, Jichi Medical School, 3311-1 Yakushiji, Minami-kawachimachi Tochigi 329-0498, Japan.
E-mail: shigeto@jichi.ac.jp
SOURCE: Biochemical and Biophysical Research Communications, (29 APR 2000), 271/1 (107-115), 37 reference(s)

CODEN: BBRCA0 ISSN: 0006-291X
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:30444864 BIOTECHNO
AB The liver is the first target organ for **malaria** parasites immediately after the bite of an infected mosquito. We studied local immunization of **malaria** DNA vaccines at the site of the liver using a gene gun as a useful tool for **in vivo** transfection of foreign genes. A **malaria** DNA vaccine consisting of the **Plasmodium** berghei circumsporozoite protein (PbCSP) gene plus the mouse IL-12 gene was bombarded directly by a gene gun into mouse liver once or into the skin twice. A marked protective effect was induced by gene bombardment into the liver (more than 71%) compared with that into the skin (less than 33%). A Th1-type immune response and high production of iNOS were observed in the hepatic lymphocytes from mice bombarded into the liver, resulting in more effective protection compared with those bombarded into the skin. These results provide an important implication on the development of efficient **malaria** vaccine strategies. (C) 2000 Academic Press.

L10 ANSWER 13 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1999:29515699 BIOTECHNO
TITLE: Hemozoin is a key factor in the induction of **malaria**-associated immunosuppression
AUTHOR: Scorza T.; Magez S.; Brys L.; De Baetselier P.
CORPORATE SOURCE: T. Scorza, Dept. Immunol. Parasitol. Ultrastr., Vlaams Interuniv. Inst. Biotechnol., Vrije Universiteit Brussel, Paardenstraat 65, 1640 Sint Genesius Rode, Belgium.
SOURCE: Parasite Immunology, (1999), 21/11 (545-554), 31 reference(s)
CODEN: PAIMD8 ISSN: 0141-9838
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29515699 BIOTECHNO
AB Infection-associated immunoincompetence during **malaria** might result from macrophage dysfunction. In the present study, we investigated the role of macrophages as target for immunosuppression during infection, using the murine **Plasmodium** c. chadaudi model. Special attention has been paid to the analysis of processing/presentation of protein antigens and presentation of peptides, using cocultures of peritoneal exudate cells (PECs) from infected mice and antigen-specific T-cell hybridomas. The results obtained indicate a defective processing of protein antigens that becomes maximal at acute parasitemias. In addition, macrophages from acutely infected mice suppress the interleukin-2 production by the antigen-activated T-cell hybridomas. This effect was independent of prostaglandin and **nitric oxide** production by the macrophage. The possible role of parasite components in the impaired accessory cell function of PECs was investigated and hemozoin, the end-product of the hemoglobin catabolism by intraerythrocytic **malaria** parasites, was found to induce similar infection-associated deficiencies in vitro. Moreover hemozoin was shown to mimic the immunosuppressive effects induced in PECs during **in-vivo** infections with P. chabaudi. In conclusion, we propose that hemozoin is a key factor in the **malaria**-associated immunosuppression, affecting both the antigen processing and immunomodulatory function of macrophages.

L10 ANSWER 14 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1999:29143428 BIOTECHNO
TITLE: A dichotomous role for **nitric oxide** in protection against blood stage **malaria**

infection
AUTHOR: Taylor-Robinson A.W.; Smith E.C.
CORPORATE SOURCE: A.W. Taylor-Robinson, Department of Biology, University of Leeds, Clarendon Way, Leeds LS2 9JT, United Kingdom.
E-mail: bgyawtr@leeds.ac.uk
SOURCE: Immunology Letters, (15 MAR 1999), 67/1 (1-9), 40 reference(s)
CODEN: IMLED6 ISSN: 0165-2478
PUBLISHER ITEM IDENT.: S0165247898001485
DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29143428 BIOTECHNO
AB **Nitric oxide** (NO) is cytotoxic and cytostatic to blood stage **malaria** parasites in vitro, but the precise mechanism(s) by which it mediates an effect **in vivo** is not known. In particular, whether or not control of acute parasitemia depends on the presence of NO is unclear. We have shown previously that blocking NO synthesis at the time of its induction may cause an increase in peak primary parasitemia during infection of mice with **Plasmodium** chabaudi, suggesting that NO may be parasiticidal **in vivo**. However, as recent data indicate that NO suppresses Th1 cell proliferation in vitro by downregulating IL-2 production, we have investigated whether this immunoregulatory function of NO affects its capacity for anti-malarial activity. Treatment of P. chabaudi-infected mice with the iNOS inhibitor aminoguanidine hemisulfate (AG) starting just prior to the peak of primary parasitemia caused a significant elevation and extension of the acute infection and led to a partial but significant abrogation of the suppression of spleen cell proliferation to both mitogen and specific antigen observed when NO synthesis was not blocked. In the absence of NO, levels of IL-2, but not of IFN-γ, TNF-α, or of any Th2-regulated cytokines examined, increased significantly. However, when AG treatment was brought forward to the early ascending phase of primary parasitemia, significantly increased levels of IFN-γ and TNF-α, as well as of IL-2, were observed over those for infected control mice similarly treated with phosphate-buffered saline. Moreover, despite the absence of NO, parasitemias of AG-treated mice were not significantly elevated. The effect of AG therefore appeared to be dependent upon the timing of its administration **in vivo**. We propose that during **malaria** infections, there is a dynamic balance between the regulatory and anti- parasitic roles of NO. While the immunosuppressive function of NO leads to a downregulation **in vivo** of production of IL-2, and indirectly of IFN-γ and TNF-α, this perceived weakening of the host cell-mediated immune response is in part masked by the protective anti-malarial effects of NO itself.

L10 ANSWER 15 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1998:28194111 BIOTECHNO
TITLE: A tumor necrosis factor mimetic peptide activates a murine macrophage cell line to inhibit mycobacterial growth in a **nitric oxide**-dependent fashion
AUTHOR: Britton W.J.; Meadows N.; Rathjen D.A.; Roach D.R.; Briscoe H.
CORPORATE SOURCE: W.J. Britton, Centenary Inst. Can. Med./Cell Biol., Newtown, NSW 2042, Australia.
E-mail: wbritton@medicine.usyd.edu.au
SOURCE: Infection and Immunity, (1998), 66/5 (2122-2127), 38 reference(s)
CODEN: INFIBR ISSN: 0019-9567
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English

AN 1998:28194111 BIOTECHNO
AB The control of mycobacterial infections depends on the cytokine-mediated activation of mononuclear phagocytes to inhibit the growth of intracellular mycobacteria. Optimal activation requires the presence of T-cell-derived gamma interferon (IFN-γ) and other signals, including tumor necrosis factor (TNF). Recently, an 11-mer peptide based on amino acids 70 to 80 of the human TNF sequence, TNF(70-80), was found to have TNF mimetic properties, which include the activation of human and mouse neutrophils to kill **Plasmodia** spp. Therefore, we investigated the capacity of TNF(70-80) to activate the murine macrophage cell line RAW264.7 infected with the vaccine strain Mycobacterium bovis bacillus Calmette-Guerin (BCG). When RAW264.7 cells were pretreated with human TNF or TNF(70-80) in the presence of IFN-γ, there was a dose-dependent reduction in the replication of BCG as measured by the uptake of .sup.3H-labeled uracil and a concomitant release of **nitric oxide** as measured by the nitrite in the culture supernatants. TNF- or TNF(70-80)-induced macrophage activation was dependent on IFN-γ and was inhibited by neutralizing monoclonal antibody to human TNF and by anti-IFN-γ antisera. Both nitrite release and BCG growth inhibition were abrogated by competitive inhibitors of L-arginine, which blocked the activation of inducible **nitric oxide** synthase. A soluble form of the Type 1 TNF receptor blocked the activation of BCG-infected macrophages by human TNF and TNF(70-80), demonstrating that the effect of TNF(70-80) is dependent on signaling through TNF receptor I. The mimetic effects of TNF(70-80) on macrophage activation in vitro suggest that treatment with TNF(70-80) may modulate mycobacterial infections **in vivo**.

L10 ANSWER 16 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1997:27138285 BIOTECHNO
TITLE: Prolonged Th1-like response generated by a **Plasmodium** yoelii-specific T cell clone allows complete clearance of infection in reconstituted mice
AUTHOR: Amante F.H.; Good M.F.
CORPORATE SOURCE: M.F. Good, Coop. Res. Ctr. for Vaccine Technol., Queensland Inst. of Medical Research, PO Royal Brisbane Hospital, Brisbane, QLD 4029, Australia.
SOURCE: Parasite Immunology, (1997), 19/3 (111-126), 37 reference(s)
CODEN: PAIMD8 ISSN: 0141-9838
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1997:27138285 BIOTECHNO
AB In the present study, we report the ability of in vitro cultured CD4.sup.+ T cells, generated following immunization with dead blood stage P. yoelii parasites, to mediate protection against homologous challenge infection in reconstituted nude mice. P. yoelii-specific T cell line cells produced IFN-γ after in vitro stimulation with specific antigen, and were protective when adoptively transferred into athymic nude mice. Following transfer of P. yoelii-specific T cell lines into nude and SCID mice, elevated levels of **nitric oxide** (NO) were detected during the first week of infection at a time when parasitaemias were suppressed. However, **in vivo** blocking of NO production through administration of L-NMMA, an inhibitor of NO synthase, increased mortality, but did not alter the course of primary parasitaemia in P. yoelii-specific T cell line-reconstituted nude mice. In addition, a P. yoelii-specific CD4.sup.+ T cell clone, which produced IFN-γ in vitro, afforded sterile protection via mechanisms other than NO. By ELISA, antibodies were undetectable on all but one day (day 79) post T cell clone transfer and parasite challenge, where very low levels of antibodies were detected, with some evidence of recognition of **malaria** proteins by Western blot. Collectively, our data suggest that T cell effector functions, independent of NO production and in the absence of high levels of parasite-specific antibodies, can contribute to sterile immunity to P. yoelii.

L10 ANSWER 17 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1996:26009339 BIOTECHNO
TITLE: **In vivo** regulation of **nitric oxide** production by tumor necrosis factor alpha and gamma interferon, but not by interleukin-4, during blood stage **malaria** in mice
AUTHOR: Jacobs P.; Radzioch D.; Stevenson M.M.
CORPORATE SOURCE: Center for Study of Host Resistance, McGill University, Montreal General Hosp. Res. Inst., 1650 Cedar Ave.,Montreal, Que. H3G 1A4, Canada.
SOURCE: Infection and Immunity, (1996), 64/1 (44-49)
CODEN: INFIBR ISSN: 0019-9567
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1996:26009339 BIOTECHNO
AB We investigated whether gamma interferon (IFN-γ; a Th1 cytokine), tumor necrosis factoe alpha (TNF-α), and interleukin-4 (IL-4; a Th2 cytokine) modulate **nitric oxide** (NO) production **in vivo** during blood stage infection with **Plasmodium** chabaudi AS. Treatment of resistant C57BL/6 mice, which resolve infection with P. chabaudi AS and produce increased levels of IFN- γ, TNF-α, and NO early during infection, with anti-IFN-γ plus anti-TNF-σ monoclonal antibodies (MAbs) resulted in a reduction of both splenic inducible NO synthase mRNA and serum NO.sub.3.sup.- levels by 50 and 100%, respectively. Treatment with the anti-TNF-α MAb alone reduced only serum NO.sub.3.sup.- levels by 35%, and treatment with the anti-IFN-γ MAb alone had no effect on NO production by these mice during infection. Susceptible A/J mice, which succumb to infection with P. chabaudi AS and produce increased levels of IL-4 but low levels of IFN-γ, TNF-α, and NO early during infection, were treated with an anti-IL-4 MAb. The latter treatment had no effect on NO production by this mouse strain during infection. In addition, our results also demonstrate that treatment of resistant C57BL/6 mice with anti-IFN-γ plus anti-TNF-α MAbs affects, in addition to NO production, other traits of resistance to P. chabaudi AS **malaria** such as the peak level of parasitemia and the development of splenomegaly. Furthermore, the change in spleen weight was shown to be an IFN-γ-independent effect of TNF-α. Treatment of susceptible A/J mice during infection with an anti-IL-4 MAb had no effect on these markers of resistance. Thus, these results demonstrate that TNF-α and IFN-γ are critical in the regulation of NO production and other traits of resistance during P. chabaudi AS **malaria** in C57BL/6 mice. These data also indicate that treatment with an anti-IL-4 antibody alone is not able to induce NO production or confer resistance to A/J mice against P. chabaudi AS **malaria**.

L10 ANSWER 18 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1995:25353607 BIOTECHNO
TITLE: **Nitric oxide** expression in the spleen, but not in the liver, correlates with resistance to blood-stage **malaria** in mice
AUTHOR: Jacobs P.; Radzioch D.; Stevenson M.M.
CORPORATE SOURCE: Center for Study of Host Resistance, Montreal Gen. Hosp. Research Inst., 1650 Cedar Avenue,Montreal, Que. H3G 1A4, Canada.
SOURCE: Journal of Immunology, (1995), 155/11 (5306-5313)
CODEN: JOIMA3 ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1995:25353607 BIOTECHNO

AB The production and function of **nitric oxide** during the early phase of blood-stage infection with **Plasmodium** chabaudi AS was analyzed using two inbred strains of mice that differ in the level of resistance to this parasite. Northern blot analysis of **in vivo** expression of inducible **nitric oxide** synthase (iNOS) revealed that early during infection resistant C57BL/6 mice, which clear the infection by 4 wk, have higher levels of iNOS mRNA in the spleen than susceptible A/J mice. In contrast, susceptible A/J mice have significantly increased levels of iNOS mRNA in the liver later in the course of infection just before death occurs. Splenic macrophages recovered from resistant C57BL/6 mice on day 7 postinfection express iNOS mRNA which is up- regulated following overnight stimulation of the cells with LPS. Furthermore, during the first week postinfection, splenic macrophages recovered from resistant hosts produce significantly higher levels of nitrite (NO.sub.2.sup.-) in vitro in response to LPS than similarly stimulated macrophages from susceptible A/J mice. Increased levels of nitrate (NO.sub.3.sup.-) were only detected in serum of resistant C57BL/6 mice at the time of peak parasitemia. Treatment with the iNOS inhibitor, aminoguanidine, reduced NO.sub.3.sup.- levels in serum of C57BL/6 mice and eliminated resistance of these hosts to P. chabaudi AS **malaria** without affecting parasitemia. These results demonstrate that the ability to produce high amounts of **nitric oxide** (NO) early during infection with blood-stage P. chabaudi AS correlates with resistance, but that NO may not be involved in parasite killing. Moreover, the tissue site of NO production, that is, spleen vs liver, appears to be critical and correlates with resistance vs susceptibility to P. chabaudi AS **malaria**, respectively.

L10 ANSWER 19 OF 25 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 95:98709 LIFESCI
TITLE: **Malaria**-specific memory T cells: Putative roles of different types of memory responses in immunity and disease
AUTHOR: Good, M.F.; Zevering, Y.
CORPORATE SOURCE: Malaria and Arbovirus Unit, Queensland Inst. Med. Res., 300 Herston Rd., Brisbane 4029, Australia
SOURCE: RES. IMMUNOL., (1994) vol. 145, no. 6, pp. 455-460. ISSN: 0923-2494.
DOCUMENT TYPE: Journal
TREATMENT CODE: General Review
FILE SEGMENT: F; K
LANGUAGE: English

AB The human memory T-cell response to **malaria** is represented by cells responsive to epitopes unique to **malaria** proteins, as well as cells which cross-react with environmental organisms. The former are identified by comparison of T-cell responses from **malaria** -exposed and non-exposed donors to short peptides representing putative epitopes. This approach has been used to calculate the lifespans of memory T cells specific for unique epitopes present on **malaria** proteins. Further, memory T-cell responses may contribute to either protection from **malaria** or disease associated with **malaria**. It is hypothesized that T cells specific for **malaria**-unique epitopes may contribute to immunity, whereas T cells specific for cross-reactive epitopes may contribute to disease. Evidence suggests that the T-cell response to **malaria** is important for both immunity and disease. Both Th1-like and Th2-like response have been shown to play significant roles in mediating immunity to blood stage parasites in animal models, the former through a **nitric-oxide**-dependent mechanism and the latter through a mechanism dependent on antibody. In humans, proliferative T-cell responses to **malaria** parasites and proteins correlate with a better outcome from **malaria** infection, and human T cells, in the presence of monocytes, can inhibit parasite growth in vitro and possibly in **vivo** in the spleen. Further, antigen-specific T cells have been shown to protect mice from challenge with **malaria** sporozoites. The lifespan of such **malaria**-specific T cells, their circulation in the body, and their specific effector functions will

influence the expression of immunity. T-cell responses may also be involved in pathology. In mouse models, cytokines have been shown to be involved in the pathogenesis of cerebral **malaria** and anaemia - the two major forms of pathology associated with **Plasmodium** falciparum, and in humans, TNF levels are related to the severity of cerebral **malaria**. TNF production may be the result of **malaria** antigens either directly stimulating monocytes or T-cell activation. T cells in **malaria**-naive individuals may also contribute to this pathology, probably due to the presence of **malaria**-specific "memory" T cells that have arisen as a result of cross-reactive stimulation. The frequency of such cells in a given individual, which in part is dependent on their lifespan, may affect the expression of pathology. In this article, we will describe a system used to identify **malaria**-specific responses and use this system to monitor the lifespans of **malaria**-specific memory T cells. The roles of **malaria**-specific memory cells in immunity and disease will then be discussed.

L10 ANSWER 20 OF 25 LIFESCI COPYRIGHT 2005 CSA on STN DUPLICATE 9
ACCESSION NUMBER: 95:8490 LIFESCI
TITLE: Induction of **nitric oxide** synthase protects against **malaria** in mice exposed to irradiated **Plasmodium** berghei infected mosquitoes: Involvement of interferon gamma and CD8 super(+) T cells
AUTHOR: Seguin, M.C.; Klotz, F.W.; Schneider, I.; Weir, J.P.; Goodbary, M.; Slayter, M.; Raney, J.J.; Aniagolu, J.U.; Green, S.J.*
CORPORATE SOURCE: EntreMed, Inc., 9610 Medical Center Dr., Suite 200, Rockville, MD 20850, USA
SOURCE: J. EXP. MED., (1994) vol. 180, no. 1, pp. 353-358. ISSN: 0022-1007.
DOCUMENT TYPE: Journal
FILE SEGMENT: F; K; W3
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Exposure of BALB/c mice to mosquitoes infected with irradiated **Plasmodium** berghei confers protective immunity against subsequent sporozoite challenge. Immunized mice challenged with viable sporozoites develop parasitemia when treated orally with substrate inhibitors of **nitric oxide** synthase (NOS). This suggests that the production of **nitric oxide** (NO) prevents the development of exoerythrocytic stages of **malaria** in liver. Liver tissue from immunized mice expressed maximal levels of mRNA for inducible NOS (iNOS) between 12 and 24 h after challenge with sporozoites. Intraperitoneal injection of neutralizing monoclonal antibody against interferon gamma (IFN- gamma) or in **vivo** depletion of CD8 super(+) T cells, but not CD4 super(+) T cells, at the time of challenge blocked expression of iNOS mRNA and ablated protection in immunized mice. These results show that both CD8 super(+) T cells and IFN- gamma are important components in the regulation of iNOS in liver which contributes to the protective response of mice immunized with irradiated **malaria** sporozoites. IFN- gamma , likely provided by **malaria**-specific CD8 super(+) T cells, induces liver cells, hepatocytes and/or Kupffer cells, to produce NO for the destruction of infected hepatocytes or the parasite within these cells.

L10 ANSWER 21 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN DUPLICATE
ACCESSION NUMBER: 1994:24279473 BIOTECHNO
TITLE: Effector mechanisms against asexual erythrocytic stages of **Plasmodium**
AUTHOR: Phillips S.
CORPORATE SOURCE: Department of Zoology, University of Glasgow,Glasgow G12 2QQ, Scotland, United Kingdom.
SOURCE: Immunology Letters, (1994), 41/2-3 (109-114) CODEN: IMLED6 ISSN: 0165-2478
DOCUMENT TYPE: Journal; Conference Article

COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1994:24279473 BIOTECHNO
AB Evidence for a role for macrophages/monocytes is largely based on in vitro not **in vivo** observations. Products of activated macrophages particularly tumor necrosis factor-alpha (TNFα) are implicated in the killing of parasites. Access of cytokines and other factors might be through intracellular channels in the infected red blood cell. The cytotoxic elements in 'crisis' serum are uncertain but may include TNF, gamma-interferon (IFNγ), and lipid peroxidases. TNFα in excess, contributes to pathology. TNF, acting as a pyrogen and raising body temperature, may moderate parasite density by killing late asexual stages. **Nitric oxide** and other nitrogen intermediates, products of activated macrophages and a number of other cell types, have been demonstrated both in vitro and **in vivo** to have a protective role. Phagocytosis of infected erythrocytes and merozoites, enhanced by the presence of immune serum in some systems, has been reported. Killing of parasites by neutrophils is enhanced by immune serum and cytokines TNFα, IFNγ and lymphotoxin. A role for natural killer cells has been suggested. Evidence for antibody-dependent cellular cytotoxicity (ADCC) is controversial. Antibody-dependent cellular inhibitory activity (ADCI) (blood monocytes plus immune IgG) has been described for P. falciparum. Evidence for an important role for complement is conflicting; an involvement in the protective activity of phagocytic cells is reported. Antibody isotypes have been relatively little studied. In murine systems IgG(2a) may have a role early in the protective immune response followed by IgG.sub.1. In P. falciparum ADCI activity is mediated by IgG.sub.1 and IgG.sub.3, two cytophilic isotypes. Antigenic variation by the asexual erythrocytic stages has been described for a number of **malaria** species and appears to serve as an immune evasion mechanism. One variant antigen has been located on the surface of trophozoite/schizont-infected erythrocytes and may be involved in cytoadherence. In P. falciparum in vitro and P. chabaudi **in vivo** antigenic switching may be at the rate of 2% per generation.

L10 ANSWER 22 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1994:25009346 BIOTECHNO
TITLE: **Nitric Oxide**: Cytokine-regulation of **nitric oxide** in host resistance to intracellular pathogens
AUTHOR: Green S.J.; Scheller L.F.; Marletta M.A.; Seguin M.C.; Klotz F.W.; Slayter M.; Nelson B.J.; Nacy C.A.
CORPORATE SOURCE: EntreMed, Inc.,Rockville, MD, United States.
SOURCE: Immunology Letters, (1994), 43/1-2 (87-94)
CODEN: IMLED6 ISSN: 0165-2478
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1994:25009346 BIOTECHNO
AB To discover how **nitric oxide** (NO) synthesis is controlled in different tissues as cells within these tissues combat intracellular pathogens, we examined three distinctively different experimental murine models designed for studying parasite-host interactions: macrophage killing of Leishmania major; nonspecific protection against tularemia (Francisella tularensis) by Mycobacterium bovis (BCG); and specific vaccine-induced protection against hepatic **malaria** with **Plasmodium** berghei. Each model parasite and host system provides information on the source and role of NO during infection and the factors that induce or inhibit its production. The in vitro assay for macrophage antimicrobial activity against L. major identified cytokines involved in-regulating NO-mediated killing of this intracellular protozoan. zoan. L. major induced the production of two competing cytokines in infected macrophages: (1) the parasite activated the gene for tumor necrosis factor (TNF), and production of TNF protein was enhanced by the presence of interferon-gamma (IFN-γ). TNF then

acted as a autocrine signal to amplify IFN-γ-induced production of NO, and (2) the parasite upregulated production of transforming growth factor-beta (TGF-β), which blocked IFN-γ-induced production of NO. Whether parasite-induced TNF (parasite destruction) or TGF-β (parasite survival) prevailed depended upon the presence and quantity of IFN-γ at the time of infection. The relationship between NO production **in vivo** and host resistance to infection was demonstrated with M. bovis (BCG). These studies confirmed that both IFN-γ and TNF are required for induction of NO-mediated nonspecific host defense **in vivo**. The presumed source of NO in these studies was the activated macrophage, however, other cells infected with parasites can also be stimulated to produce NO. In studying acquired immunity to **malaria** induced by irradiated sporozoites, we found that IFN-γ provided by **malaria**-specific CD8.sup.+ T cells stimulated sporozoite-infected hepatocytes to produce NO for destruction of either infected hepatocytes or the parasite, P. berghei, within these cells.

L10 ANSWER 23 OF 25 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 1993:23101073 BIOTECHNO
TITLE: **In vivo** induction of the **nitric oxide** pathway in hepatocytes after injection with irradiated **malaria** sporozoites, **malaria** blood parasites or adjuvants
AUTHOR: Nussler A.K.; Renia L.; Pasquetto V.; Miltgen F.; Matile H.; Mazier D.
CORPORATE SOURCE: Department of Surgery, University of Pittsburgh,Pittsburgh, PA 15261, United States.
SOURCE: European Journal of Immunology, (1993), 23/4 (882-887)
CODEN: EJIMAF ISSN: 0014-2980
DOCUMENT TYPE: Journal; Article
COUNTRY: Germany, Federal Republic of
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1993:23101073 BIOTECHNO
AB The mechanisms responsible for malarial immunity induced by repetitive injections of X-irradiated sporozoites have not been fully established. We demonstrate here that a single injection of irradiated sporozoites induced, as soon as 24 h after, a non-permissive state to hepatocyte reinfection with sporozoites in vitro. The same effect was observed when malarial blood forms, irradiated promastigotes of Leishmania infantum, adjuvants (muramyl dipeptide, poly acidylic uridylic) or interferon-γ was injected. Activation of the **nitric oxide** (NO) pathway in the hepatocyte by these factors was found to be responsible for hepatocyte refractory status. Additionally, this metabolic pathway is involved in protection given by repeated injections of irradiated sporozoites since protection could be reversed by treating mice at the time of sporozoite challenge with a competitive inhibitor (N(G)-monomethyl-L-arginine) of the NO pathway. These results suggest that, in view of an antisporozoite vaccine, further studies are needed to find out how to activate specifically a long-lasting nonspecific immune response.

L10 ANSWER 24 OF 25 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 94:15921 LIFESCI
TITLE: Factors regulating natural transmission of **Plasmodium** berghei to the mosquito vector, and the cloning of a transmission-blocking immunogen
AUTHOR: Sinden, R.E.; Barker, G.C.; Paton, M.J.; Fleck, S.L.; Butcher, G.A.; Waters, A.; Janse, C.J.; Rodriguez, M.H.
CORPORATE SOURCE: Dep. Biol., Imperial Coll., London SW7 2BB, UK
SOURCE: PARASSITOLOGIE, (1993) pp. 107-112.
Meeting Info.: Commission of the European Communities Second Malaria Contract Holders Meeting. Orvieto, Italy. 20-22 Mar 1992.
ISSN: 0048-2951.

DOCUMENT TYPE: Book
TREATMENT CODE: Conference
FILE SEGMENT: K; F; G; Z; W3
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Naturally occurring factors that regulate the infectivity of P. berghei infected rodent hosts to the mosquito vector in **vivo** have been compared in T.O., Balb/C and immunodeficient SCID mice. No detectable differences in infectivity were observed suggesting B and T cell mediated factors are not involved. Further studies investigated roles for macrophage colony stimulating factors, the cytokines IFN gamma and TNF alpha , of neutrophils, and of **nitric oxide** in the SCID mouse, but have failed to demonstrate an important role in **vivo** for any factor examined. Differences between these results and those obtained in vitro on the human and primate parasites must therefore be explained by biological differences between the parasite/host combinations, or by technical differences in experimental designs. Induced immunity to the ookinete surface antigen Pbs 21 of P. berghei can totally block the transmission of the parasite from the gametocyte infected host to the vector. We have cloned the gene encoding Pbs 21 and shown it bears striking structural similarities to Pfs 25, Pgs 25 and more particularly Pgs 28 in that it has a high cysteine content (9.5%), 4 EGF-like domains and hydrophobic amino-"signal"- and carboxyl-"anchor" sequences. The encoding gene is on chromosome 5 and is found also in P. chabaudi, P. yoelii and P. vinckei.

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TITLE: **In vivo** induction of nitrite and nitrate by tumor necrosis factor, lymphotoxin, and interleukin-1: Possible roles in **malaria**
AUTHOR: Rockett K.A.; Awburn M.M.; Aggarwal B.B.; Cowden W.B.; Clark I.A.
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AB Tumor necrosis factor and related cytokines are thought to be implicated in cell-mediated immunity and pathophysiology in **malaria**, but their mechanism of action has not been ascertained. Tumor necrosis factor has been reported to generate **nitric oxide** in vitro, so we have measured levels of this molecule and its products in the plasma of mice after they have received an injection of tumor necrosis factor, lymphotoxin, interleukin-1, gamma interferon, or interleukin-6, all of which have been reported to be increased in **malaria**. Total reactive nitrogen intermediate levels in plasma were assayed spectrophotometrically after exposing plasma to a copper-cadmium-zinc catalyst to convert nitrate to nitrite and then to Griess reagent. Tumor necrosis factor, lymphotoxin, and interleukin-1 all induced reactive nitrogen intermediates **in vivo**, with interleukin-1 showing the most activity. Tumor necrosis factor was then examined more closely. It induced more reactive nitrogen intermediates in **malaria**-infected mice than in normal mice, and appreciably more was in the form of nitrate than was in the form of nitrite. N(G)-methyl-L-arginine inhibited the **in vivo** generation of reactive nitrogen intermediates by tumor necrosis factor in a dose-dependent manner, implying that these molecules were arginine derived. These results are consistent with the possibility that tumor necrosis factor, lymphotoxin, and interleukin-1 may contribute to host pathology and parasite suppression through generation of **nitric oxide**.